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# Abstract LB-366: Everolimus (EV) potentiates Sorafenib (SOR)activity in osteosarcoma (OS) preclinical models: a combination targeting the crosstalk between ERK1/2 and mTORC1/2 signaling pathways

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## Abstract

OS is the most frequent primary bone tumor in children and young adults.The mammalian Target of Rapamycin (mTOR) and the Extracellular Regulated Kinases (ERK)1/2 pathways have been shown to cooperate in survival advantage of OS. Inhibition of this signaling can be a rational pharmacological strategy to impinge on OS progression. This study pursued the dual blockage of ERK1/2 and mTOR pathways by combining the multikinase inhibitor SOR with the rapamycin analog EV. The synergistic anti-profilerative effect was found against 5 out 7 OS cell lines (combination index<1, based on Chou-Talalay method). The inhibition of OS colony growth, due to cell cycle arrest and apoptosis induction was obtained. Mechanistically SOR alone, but EV, inhibited phospho-ERK1/2. EV and SOR as single

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agent induced the down-regulation of P-S6, P-4EBP. EV alone induced an increase in phospho-AKT as a consequence of the release of negative feed back by MTORC1 on MTORC2. Nonetheless, the combined treatment completely abrogated both ERK1/2 and MTORC1/2. The crosstalk among these pathways was interrupted by AMPK activation due to sorafenib-induced ROS burst and MTORC2 disassembling. The anti-tumoral activity and the inhibition of angiogenesis and metastasis in vivo were demonstrated against OS xenografts in NOD/SCID mice and in chicken chorioallantoic membrane model. A 28 daily oral gavage of mice (6/group) with SOR 5mg/kg, EV 1mg/kg, or their combination reduced tumor growth to 34%, 46%, and 29% of control slowing down cell proliferation and inducing apoptosis. In vivo model of OS metastasis obtained by e.v injection of OS cells confirmed the high metastatic potential of human OS consistently with the clinical experience. However, daily treatment of mice induced a significant reduction in number and size of lung metastases (foci area 65%, 74% and 29% of control obtained after 14 daily SOR, EV, and combined treatment). Anti-migratory effect was evidenced in 7 OS cell lines and was attributable to SRC/FAK/ERM pathway inhibition. HUVEC branching morphogenesis inhibition and reduction of blood vessel density in xenografts confirmed a strong potentiation of anti-angiogenic activity of drug combination. These results straighten our understanding of the networking nature of oncogenic signal transduction circuits in OS, therefore sustaining the rational for testing combination of sorafenib and everolimus in clinical setting.

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